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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/645,659	08/22/2003	Oron Yacoby-Zeevi	26128	8084

7590 03/20/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
03/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/645,659	YACOBY-ZEEVI ET AL.	
	Examiner	Art Unit	
	MARIANNE DIBRINO	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/22/06, 3/23/07, 8/2/06, 6/23/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/5/07, 11/15/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,5,6,9,19-35,45,46,55-59,63,64,67,77-93,113-117,120,130,133,135-151,160,161,171-175,178,188,191-208,217,218,228-233,236,237,241-251,255,256,260-271,274,279-291,294,295,299-318,321,326-341,345,346,350-355,359,360 and 364-370.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 20,22,26,27,29,33,34,58,78-80,84,85,87,91,92,135-138,140-143,147-150,174,192-195,197-200,202, 204-207,232,233,236,237,241-251,255,256,260-271,274,279-291,294,295,299-318,321,326-340.

Continuation of Disposition of Claims: Claims rejected are 1,5,6,9,19,21,23-25,28,30-32,35,45,46,55-57,59,63,64,67,77,81-83,86,88-90,93,113-117,120,130,133,139,144,146,151,160,161,171-175,178,188,191,196,201,203,208,217,218,228-231,341,345,346,350-355,359,360 and 364-370.

DETAILED ACTION

1. Applicant's amendment and response filed 11/22/06 and Applicant's responses filed 3/23/07, 8/2/06 and 6/23/04 are acknowledged and have been entered.

2. Applicant's election of Group I (originally filed claims 1, 5, 6, 9, 19, -231 and 341-370), and species of chemically inert, insoluble carrier that is a gel polymer as the affinity medium in Applicant's said response filed 8/2/06, and the species of full length mononospecific monoclonal antibody that is capable of binding to at least one epitope of a heparanase protein that is at least 90% homologous to SEQ ID NO:4, said epitope being at least 90% homologous to SEQ ID NO: 9, and wherein said epitope is a catalytic nucleophilic sequence of a heparanase protein, said antibody being HP3/17 in Applicant's responses filed 11/22/06 and 3/23/07 is acknowledged.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 1, 5, 6, 9, 28, 35, 45, 46, 55-57, 59, 63, 64, 67, 86, 93, 113-115, 117, 120, 130, 133, 144, 151, 160, 161, 171-173, 175, 178, 188, 191, 201, 208, 217, 218, 228-230, 341, 345, 350, 351, 353-355, 359, 360, 364, 365, 367-370 read on the elected species.

Upon consideration of Applicant's IDS reference WO 00/25817 A1, the species of anti-heparanase antibodies in claims 19, 23-25, 31-32, 77, 81-83, 88-90, 116, 366 and 367 are also being included in examination. Upon consideration of art reference US 20030236215 A1, the species of affinity purified polyclonal antibody is being included in this examination.

Accordingly, claims 20, 22, 26, 27, 29, 30, 33, 34, 58, 78-80, 84, 85, 87, 91, 92, 116, 135-139, 140-143, 146-150, 174, 192-196, 197-200, 202-207, 352 (non-elected species of Group I) and claims 231-233, 236, 237, 241-251, 255, 256, 260-271, 274, 279-291, 294, 295, 299-318, 321, 326-340 (non-elected Groups II and III) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1, 5, 6, 9, 19, 21, 23-25, 28, 31, 32, 35, 45, 46, 55-57, 59, 63, 64, 67, 77, 81-83, 86, 88-90, 93, 113-117, 120, 130, 133, 139, 144, 146, 151, 160, 161, 171-175. 178, 188, 191, 201, 203, 208, 217, 218, 228-231, 341, 345, 350, 351, 353-355, 359, 360, 364, 365, 366-370 are currently being examined.

3. Color photographs and color drawings are not accepted unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2).

Applicant has only submitted one set of the color drawings, and has not amended the first paragraph of the brief description of the drawings section of the instant specification as enunciated supra.

4. The use of the trademarks PROSTASCINT and HUMASPECT (for example on page 8 at line 6) have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 5, 6, 9, 23-25, 30-32, 35, 45, 46, 55, 56, 59, 63, 64, 67, 81-83, 86, 88-90, 93, 113, 114, 116, 117, 120, 130, 133, 151, 160, 161, 171, 172, 341, 345, 350, 355, 359, 360, 364, 366, 369 and 370 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicant has claimed a broad genus of an isolated antibody or portion thereof (and composition thereof) *capable of specifically binding to at least one epitope* of a heparanase protein, said heparanase protein being at least 90% homologous to the amino acid sequence of SEQ ID NO: 4, and including the limitations recited in dependent claims.

The claims encompass an isolated antibody or portion thereof that is capable of specifically binding more than one epitope of a heparanase protein that is at least 90% homologous to the amino acid sequence of SEQ ID NO: 4. Applicant has not adequately described the subgenus of isolated antibody or portion thereof that is capable of specifically binding to more than one epitope of a heparanase protein, said heparanase protein being at least 90% homologous to the amino acid sequence of SEQ ID NO: 4.

The specification discloses isolated monoclonal antibodies that can bind to one epitope of heparanase protein.

It is known in the art that specificity of an antibody is defined by its ability to discriminate between the antigen against which it was made and any other antigens, selectivity is the ability of an antibody to discriminate in an all-or-none manner, between two related ligands, and cross-reactivity is defined as the ability to react with related ligands other than the immunogen (Evidentiary reference Paul, W. E. Fundamental Immunology, 5th Edition, Lippincott Williams & Wilkins, Philadelphia, 2003, pages 86-89). It is also known in the art that a polyclonal antiserum contains multiple antibodies with different epitope-binding specificities; however, these antibodies are not “an isolated antibody” as is recited in the instant claims.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Applicant

was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, January 5, 2001, see especially page 1106 column 3).

In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) 19 F. 3d 1559, the court noted: "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."
The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

As discussed above, the structure of the isolated antibody or portion thereof capable of specifically binding to more than one epitope of a heparanase protein having at least 90% homology to SEQ ID NO: 4 is not disclosed. Therefore, it appears that the broad genus of antibodies claimed by Applicant lacks adequate written description because there does not appear to be any disclosed correlation between structure of the heparanase protein bound by the antibody and the function of the antibody in being capable of specifically binding more than one epitope of said protein. Further, the examples of antibodies disclosed in the specification are not representative of the claimed genus because they are monoclonal antibodies that bind one epitope of the said protein, whereas the breadth of the claims reads on an isolated antibody binding to more than one epitope on the protein. As such a skilled artisan would reasonably conclude that Applicant was not in possession of the full breadth of the claimed genus of antibodies.

9. Claims 353 and 367 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the monoclonal antibodies HP130, HP 239, HP 108.264, HP 115.140, HP 152.197, HP 110.662, HP 144.141, HP 108.371, HP135.108, HP 151.316, HP 117.372, HP 37/33 and HP3/17 are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell line which produces this antibody. See 37 CFR 1.801-1.809.

If the deposit was made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicants, assignees or a statement by an attorney of record over his or her signature and registration number stating that the deposit has been made under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application is required.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. 1.801-1.809, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(A) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(B) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(C) the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent whichever is longer;

(D) a viability statement in accordance with the provisions of 37 C.F.R. 1.807;

(E) the deposit will be replaced should it become necessary due to inviability, contamination, or loss of capability to function in the manner described in the specification.

Furthermore, unless the deposit was made at or before the time of filing, a declaration filed under 37 C.F.R. 1.132 is necessary to construct a chain of custody. Hybridoma…producing antibody… was deposited after the time of filing. The declaration, executed by a person in a position to know, should identify the deposited hybridoma by its depository accession number, establish that the deposited hybridoma is the same as that described in the specification, and establish that the deposited hybridoma was in Applicant's possession at the time of filing. *In re Lundak*, 27 USPQ 90.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

NOTE THE CURRENT ATCC DEPOSITORY ADDRESS
American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

11. Claims 5, 130, 353 and 367 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 353 and 367 are indefinite in the recitation of HP130, HP 239, HP 108.264, HP 115.140, HP 152.197, HP 110.662, HP 144.141, HP 108.371, HP135.108, HP 151.316, HP 117.372, HP 37/33 and HP3/17 because their characteristics are not known. The use of "HP130, HP239, HP 108.264, HP 115.140, HP 152.197, HP 110.662, HP 144.141, HP 108.371, HP135.108, HP 151.316, HP 117.372, HP 37/33 and HP3/17" as the sole means of identifying the claimed monoclonal antibodies renders the claim indefinite because "HP130, HP239, HP 108.264, HP 115.140, HP 152.197, HP 110.662, HP 144.141, HP 108.371, HP135.108, HP 151.316, HP 117.372, HP 37/33 and HP3/17" are merely laboratory designations which do not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct monoclonal antibodies.

b. Claim 5 is indefinite in the recitation of "as set forth in any of SEQ ID NO: 4" because it is not clear what is meant.

c. Claim 130 is indefinite in the recitation of "wherein said heparanase protein is at least 90% homologous to the amino acid sequence of SEQ ID NO: 9" because it is not clear what is meant, *i.e,* SEQ ID NO: 9 is an epitope peptide subsequence of the heparanase protein consisting of SEQ ID NO: 4.

d. Claim 367 recites the limitation "the pharmaceutical composition of claim 366 comprising a monoclonal antibody" selected from among the recited monoclonal antibodies. There is insufficient antecedent basis for this limitation in the claim because the anti-heparanase antibody of base claim 366 is a humanized antibody, whereas the antibodies recited in claim 367 are not humanized as evidenced by evidentiary references InSight "Clone HP3/17" and Insight "Clone HP130".

12. For the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of the instant application, *i.e.,* 8/22/03, as the parent applications do not support the claimed limitations of the instant application. At minimum, the art references do not have support for an isolated antibody or portion thereof capable of specifically binding to at least one epitope of a heparanase protein being at least 90% homologous to the amino acid sequence of SEQ ID NO: 4. The Examiner notes that parent application serial no. 10/456,573 does not have support for the following limitations: portion of an antibody, and the heparanase protein consisting of the sequence of SEQ ID NO: 4 of the instant claims.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 1, 19, 23-25, 28, 30-32, 55, 56, 57, 59, 77, 81-83, 86, 88-90, 113-116, 341, 345, 351, 353, 355, 359 and 365-367 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/25817 A1 (IDS reference).

WO 00/25817 A1 teaches anti-heparanase monoclonal antibodies HP-130 and HP-239 that were produced against heparanase protein consisting of SEQ ID NO: 2 that is 99.9% identical to SEQ ID NO: 4 of the instant claims (*i.e.,* the difference is amino acid residue 246 is "Y" in SEQ ID NO: 2 and "F" in SEQ ID NO: 4), and pharmaceutical composition thereof. HP-130 recognizes a segment

of 79 amino acid residues of the C-terminus of the heparanase open reading frame, amino acid residues 465-453, and HP-239 recognizes an internal epitope localized to amino acid residues 130-230. WO 00/25817 A1 teaches hybridomas producing anti-heparanase monoclonal antibodies, polyclonal antibodies and fragments of either polyclonal or monoclonal antibodies such as Fab or single chain antibodies (see especially abstract, page 8 at lines 21-31, page 9 at lines 9-23, page 10 at lines 20-32, page 15 at the first seven paragraphs, claims 21-23).

Claims 55, 56, 113 and 114 are included in this rejection because the recitation of how the heparanase protein is purified or made carries no patentable weight in these product claims.

Claims 57 and 115 are included in this rejection because the art reference inherently teaches the hybridoma that produces the monoclonal antibody.

15. Claims 1, 5, 6, 19, 9, 21, 28, 35, 45, 46, 55, 56, 57, 59, 63, 64, 67, 77, 86, 93, 113, 114, 115, 117, 120, 130, 133, 144, 151, 160, 161, 171, 172, 173, 175, 178, 188, 191, 201, 208, 217, 218, 228, 229 and 230 are rejected under 35 U.S.C. 102(e) as being anticipated by US 20030236215 A1 (publication of application serial no.10/456,573) as evidenced by U.S. Patent No. 6,177,545.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

US 20030236215 A1 discloses the monoclonal antibody 3/17 that was raised against synthetic peptide pep9 (RPGKKVWLGETSSAY) that is identical to SEQ ID NO: 9 of the instant claims, said peptide contains the catalytic nucleophilic residue of the active site of heparanase that is 99.9% identical to the heparanase consisting of SEQ ID NO: 4 of the instant claims [0322]. US 20030236215 A1 also discloses an affinity purified polyclonal anti-heparanase antibody as described in U.S. patent application serial no. 09/071,739, *i.e.,* U.S. Patent No. 6,177,545.

Evidentiary reference U.S. Patent No. 6,177,545 discloses a heparanase protein SEQ ID NO: 2, that is 99.9% identical to SEQ ID NO: 4 of the instant claims

Claims 55, 56, 113, 114, 171, 172, 228 and 229, are included in this rejection because the recitation of how the heparanase protein is purified or made carries no patentable weight in these product claims.

Claims 57, 115, 173 and 230 are included in this rejection because the art reference inherently teaches the hybridoma that produces the monoclonal

antibody 3/17 as the art reference discloses that the said antibody is a monoclonal antibody that was raised against synthetic peptide pept9.

Claim 5 is included in this rejection because both the art heparanase and the heparanase of the instant claims contains peptide 9 against which the art antibody was generated and which both antibodies specifically bind to.

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1, 23, 28, 30, 57-59, 81, 86, 88, 115-117, 139, 144, 146, 173-175, 196, 201, 230, 231, 341, 345, 346, 350-355, 359, 360, 364, 365, 367 and 368 are rejected under 35 U.S.C. 103(a) as being obvious over US 20030236215 A1 in view of Bendig (METHODS: A Companion to Methods in Enzymology. 8: 83-93, 1995).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

US 20030236215 A1 discloses the monoclonal antibody 3/17 that was raised against synthetic peptide pep9 (RPGKKVWLGETSSAY) that is identical to SEQ ID NO: 9 of the instant claims, said peptide contains the catalytic nucleophilic residue of the active site of heparanase that is 99.9% identical to the heparanase consisting of SEQ ID NO: 4 of the instant claims [0322]. US 20030236215 A1 further disclose that antibodies specific for heparanase are expected to be in common use in basic research of such conditions as autoimmunity, renal failure, metastatic cancer, inflammation, angiogenesis, restenosis, atherosclerosis, neurodegenerative diseases and viral infections [0025]. US 20030236215 A1 discloses pharmaceutical compositions comprising either DNA encoding heparanase or heparanase protein for eliciting antibody production including *in vivo* for combating inflammatory reactions and cancer, and further comprising a pharmaceutically acceptable carrier [0185], [0189], [0200].

US 20030236215 A1 does not disclose the antibody in a pharmaceutical composition.

Bendig teaches that clinical results with rodent antibodies with possible therapeutic applications in humans has been disappointing primarily because rodent antibodies are highly immunogenic in humans. Bendig further teaches that partial or full humanization has helped to overcome this problem (especially abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have formulated the monoclonal antibody 3/17 in a pharmaceutical composition. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have humanized the antibody disclosed by US 20030236215 A1 as per the teaching of Bendig and to have formulated it in a pharmaceutical composition.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat the conditions disclosed by US 20030236215 A1 by passive administration of an anti-heparanase monoclonal antibody of defined specificity, that against the catalytic nucleophilic active site of the heparanase enzyme, similar to active elicitation of anti-heparanase antibodies using a pharmaceutical composition comprising DNA as disclosed by US 20030236215 A1, and to have reduced immunogenicity as taught by Bendig.

The instant claims 353 and 367 are included in this rejection because while US 20030236215 A1 does not disclose that monoclonal antibody 3/17 is monoclonal antibody HP 3/17 recited in the instant claims, it does disclose that the monoclonal antibody was elicited by the same peptide pep9 for the HP 3/17 monoclonal antibody recited in the said claims.

Therefore the claimed antibody appears to be the similar to the antibody of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the antibody of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

18. Claims 1, 369 and 370 are rejected under 35 U.S.C. 103(a) as being obvious over US 20030236215 A1 in view of Pontremoli *et al* (PNAS USA 76(2): 6323-6325, 1979).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

US 20030236215 A1 discloses the monoclonal antibody 3/17 that was raised against synthetic peptide pep9 (RPGKKVWLGETSSAY) that is identical to SEQ ID NO: 9 of the instant claims, said peptide contains the catalytic nucleophilic residue of the active site of heparanase that is 99.9% identical to the heparanase consisting of SEQ ID NO: 4 of the instant claims [0322]. US 20030236215 A1 further disclose that antibodies specific for heparanase are expected to be in common use in basic research of such conditions as autoimmunity, renal failure, metastatic cancer, inflammation, angiogenesis, restenosis, atherosclerosis, neurodegenerative diseases and viral infections [0025]. US 20030236215 A1 discloses that anti-heparanase antibodies may be applied for immunodetection and diagnosis of the various conditions in biopsy specimens, plasma samples and body fluids [0025]. US 20030236215 A1 discloses screening biological samples for heparanase activity [0007]-[0009].

US 20030236215 A1 does not disclose the antibody is immobilized on a chemically inert carrier that is a gel polymer.

Pontremoli *et al* teach Sepharose (*i.e.,* a gel polymer) coupled –anti-aldolase antibody is used to adsorb and elute aldolase enzyme for subsequent measurement of specific activity of the enzyme, *i.e.,* by measuring activity in crude extracts *versus* the amount of protein eluted from the antibody-Sepharose column (see entire reference).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have coupled the 3/17 antibody disclosed by US 20030236215 A1 to Sepharose beads, similar to the antibody-Sepharose beads taught by Pontremoli *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to isolate heparanase disclosed by US 20030236215 A1 from biological samples as per the teaching of Pontremoli *et al*

for isolating another enzyme and calculating its specific activity by measuring activity in crude extracts and the amount of protein eluted from the antibody-Sepharose column.

19. Claims 1, 369 and 370 are rejected under 35 U.S.C. 103(a) as being obvious over WO 00/25817 A1 in view of Pontremoli *et al* (PNAS USA 76(2): 6323-6325, 1979).

WO 00/25817 A1 teaches anti-heparanase monoclonal antibodies HP-130 and HP-239 that were produced against heparanase protein consisting of SEQ ID NO: 2 that is 99.9% identical to SEQ ID NO: 4 of the instant claims (*i.e.,* the difference is amino acid residue 246 is "Y" in SEQ ID NO: 2 and "F" in SEQ ID NO: 4), and pharmaceutical composition thereof. HP-130 recognizes a segment of 79 amino acid residues of the C-terminus of the heparanase open reading frame, amino acid residues 465-453, and HP-239 recognizes an internal epitope localized to amino acid residues 130-230. WO 00/25817 A1 teaches using the antibodies to inhibit heparanase activity (see especially abstract, page 8 at lines 21-31, page 9 at lines 9-23, page 10 at lines 20-32, page 15 at the first seven paragraphs, claims 21-23).

WO 00/25817 A1 does not teach that the antibody is immobilized on a chemically inert carrier that is a gel polymer.

Pontremoli *et al* teach Sepharose (*i.e.,* a gel polymer) coupled –anti-aldolase antibody is used to adsorb and elute aldolase enzyme for subsequent measurement of specific activity of the enzyme, *i.e.,* by measuring activity in crude extracts *versus* the amount of protein eluted from the antibody-Sepharose column (see entire reference).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have coupled the anti-heparanase monoclonal antibody taught by WO 00/25817 A1 to Sepharose beads, similar to the antibody-Sepharose beads taught by Pontremoli *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to isolate heparanase taught by WO 00/25817 A1 from biological samples as per the teaching of Pontremoli *et al* for isolating another enzyme and calculating its specific activity by measuring activity in crude extracts and the amount of protein eluted from the antibody-Sepharose column.

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where

the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1, 5, 9, 28, 35, 45, 46, 55-57, 59, 63, 64, 67, 86, 93, 113-115, 117, 120, 130, 133, 144, 151, 160, 161, 171-173, 175, 178, 188, 191, 201, 208, 217, 218, 228-230, 341, 345, 346, 350, 351, 353-355, 359, 360, 364, 365, 367-370 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4, 5, 8, 9, 27, 28, 31, 32, 145, 146, 150, 151, 154, 155, 159, 164, 165, 168 and 169 of copending Application No. 10/559,925 in view of Campbell.

This is a provisional obviousness-type double patenting rejection.

Exclusive of claims 154 and 168, the claims of 10/559,925 recite an isolated antibody, but do not recite that the antibody is a monoclonal antibody.

Campbell teaches that it is routine to make monoclonal antibodies against a macromolecule, sometimes without a clear objective for their use, and teach hybridoma technology (section 1.3.4 on page 29 and pages 1-4).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a monoclonal version of the antibodies recited in the claims of 10/559,925 as per the teaching of Campbell by making hybridomas to produce the said monoclonal antibodies.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Campbell teach it is routine to make

monoclonal antibodies to any macromolecule, sometimes without a clear objective for their use.

Instant claims 55, 56, 113, 114, 171, 172, 228 and 229, are included in this rejection because the recitation of how the heparanase protein is purified or made carries no patentable weight in these product claims.

22. Claims 1, 5, 9, 28, 35, 45, 46, 55-57, 59, 63, 64, 67, 86, 93, 113-115, 117, 120, 130, 133, 144, 151, 160, 161, 171-173, 175, 178, 188, 191, 201, 208, 217, 218, 228-230, 341, 345, 346, 350, 351, 353-355, 359, 360, 364, 365, 367-370 are provisionally rejected under 35 U.S.C. 103(a) as being obvious over copending Application No. 10/559,925 which has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e) if published or patented. This provisional rejection under 35 U.S.C. 103(a) is based upon a presumption of future publication or patenting of the conflicting application.

This provisional rejection might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by a showing of a date of invention for the instant application prior to the effective U.S. filing date of the copending application under 37 CFR 1.131. This rejection might also be overcome by showing that the copending application is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

23. Claims 1, 5, 9, 23, 28, 31, 35, 45, 46, 55-57, 59, 63, 64, 67, 81, 86, 88, 93, 113-117, 120, 130, 133, 144, 151, 160, 161, 171-173, 175, 178, 188, 191, 201, 208, 217, 218, 228-230, 341, 345, 346, 350-355, 359, 360, 364, 365-370 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 10-27 of U.S. Patent No. 6,562,950 B2 in view of US 20030236215 A1.

The claims of U.S. Patent No. 6,562,950 B2 recite a monoclonal antibody and pharmaceutical composition thereof, wherein the monoclonal antibody is elicited by at least one epitope of a heparanase protein having an amino acid sequence as set forth in SEQ ID NO: 1, said SEQ ID NO: 1 being 99.9% identical to SEQ ID NO: 4 of the instant claims.

Claims 1-6 and 10-27 of U.S. Patent No. 6,562,950 B2 do not recite wherein the antibody is elicited by or capable of binding to at least one epitope of a heparanase protein being at least 90% homologous to the amino acid sequence of SEQ ID NO: 4 of the instant application, the at least one epitope consisting of or being at least 90% homologous to SEQ ID NO: 9 of the instant claims.

US 20030236215 A1 discloses the monoclonal antibody 3/17 that was raised against synthetic peptide pep9 (RPGKKVWLGETSSAY) that is identical to SEQ ID NO: 9 of the instant claims, said peptide contains the catalytic nucleophilic residue of the active site of heparanase that is 99.9% identical to the heparanase consisting of SEQ ID NO: 4 of the instant claims [0322].

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the monoclonal antibody recited in the claims of U.S. Patent No. 6,562,950 B2 with specificity for the peptide taught by US 20030236215 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because US 20030236215 A1 discloses that the said peptide contains the catalytic nucleophilic residue of the active site of heparanase that is 99.9% identical to the heparanase consisting of SEQ ID NO: 4 of the instant claims.

Claims 55, 56, 113, 114, 171, 172, 228 and 229, are included in this rejection because the recitation of how the heparanase protein is purified or made carries no patentable weight in these product claims.

24. Claims 1, 5, 9, 23, 28, 31, 35, 45, 46, 55-57, 59, 63, 64, 67, 81, 86, 88, 93, 113-117, 120, 130, 133, 144, 151, 160, 161, 171-173, 175, 178, 188, 191, 201, 208, 217, 218, 228-230, 341, 345, 346, 350-355, 359, 360, 364, 365-370 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,652,950 B2. The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention “by another”; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

25. Claims 1, 5, 9, 19, 21, 28, 35, 45, 46, 55-57, 59, 63, 64, 67, 86, 93, 113-115, 117, 120, 130, 133, 144, 151, 160, 161, 171-173, 175, 178, 188, 191, 201, 208, 217, 218, 228-230, 341, 345, 346, 350, 351, 353-355, 359, 360, 364, 365, 367-370 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,177,545 in view of US 20030236215 A1.

The claims 1-9 of U.S. Patent No. 6,177,545 recite a monoclonal antibody specifically binding at least one epitope of a heparanase protein having an amino acid sequence as set forth in SEQ ID NO: 2 which is 99.9% identical to SEQ ID NO: 4 of the instant claims.

Claims 1-9 of U.S. Patent No. 6,177,545 do not recite wherein the antibody is elicited by or capable of binding to at least one epitope of a heparanase protein being at least 90% homologous to the amino acid sequence of SEQ ID NO: 4 of the instant application, the at least one epitope consisting of or being at least 90% homologous to SEQ ID NO: 9 of the instant claims.

US 20030236215 A1 discloses the monoclonal antibody 3/17 that was raised against synthetic peptide pep9 (RPGKKVWLGETSSAY) that is identical to SEQ ID NO: 9 of the instant claims, said peptide contains the catalytic nucleophilic residue of the active site of heparanase that is 99.9% identical to the heparanase consisting of SEQ ID NO: 4 of the instant claims [0322].

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the monoclonal antibody recited in the claims of U.S. Patent No. 6,177,545 with specificity for the peptide taught by US 20030236215 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because US 20030236215 A1 discloses that the said peptide contains the catalytic nucleophilic residue of the active site of heparanase that is 99.9% identical to the heparanase consisting of SEQ ID NO: 4 of the instant claims.

Claims 55, 56, 113, 114, 171, 172, 228 and 229, are included in this rejection because the recitation of how the heparanase protein is purified or made carries no patentable weight in these product claims.

26. Claims 1, 5, 9, 19, 21, 28, 35, 45, 46, 55-57, 59, 63, 64, 67, 86, 93, 113-115, 117, 120, 130, 133, 144, 151, 160, 161, 171-173, 175, 178, 188, 191, 201, 208, 217, 218, 228-230, 341, 345, 346, 350, 351, 353-355, 359, 360, 364, 365, 367-370 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,177,545. The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

27. No claim is allowed.

28. With regard to Applicant's Form 1449 filed 1/5/07:

- Pages 1-3 have been crossed out because the references can not be located, and the reference citations have check marks next to them.
- The last six pages have been crossed out because Applicant has submitted IDS references that have already been initialed and dated prior to submission of the said Form 1449. These pages of Applicant's IDS listing includes a copy of an initialed IDS listing from another application, thus the IDS listing does not comply with the requirements under 37 C.F.R. 1.98(a)(1).
- Other references crossed out on Applicant's said Form 1449 have not been considered because they can not be located.

29. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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March 13, 2008

/G.R. Ewoldt/
Primary Examiner, Art Unit 1644